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MAJOR ARTICLE

Evaluation of Clinical Outcomes After Introduction of a Dedicated Infectious Diseases–Critical Care Medicine Service in Critical Care Units

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Background. Infection is a leading cause of admission to intensive care units (ICUs), with critically ill patients often receiving empiric broad-spectrum antibiotics. Nevertheless, a dedicated infectious diseases (ID) consultation and stewardship team is not routinely established. An ID–critical care medicine (ID-CCM) pilot program was designed at a 400-bed tertiary care hospital in which an ID attending was assigned to participate in daily rounds with the ICU team, as well as provide ID consultation on select patients. We sought to evaluate the impact of this dedicated ID program on antibiotic utilization and clinical outcomes in patients admitted to the ICU.

Methods. In this single-site retrospective study, we analyzed antibiotic utilization and clinical outcomes in patients admitted to an ICU during the postintervention period from January 1 to December 31, 2017, and compared it to antibiotic utilization in the same ICUs during the preintervention period from January 1 to December 31, 2015.

Results. Our data showed a statistically significant reduction in usage of most frequently prescribed antibiotics including vancomycin, piperacillin-tazobactam, and cefepime during the intervention period. When compared to the preintervention period there was no difference in-hospital mortality, hospital length of stay, and readmission.

Conclusions. With this multidisciplinary intervention, we saw a decrease in the use of the most frequently prescribed broad-spectrum antibiotics without a negative impact on clinical outcomes. Our study shows that the implementation of an ID-CCM service is a feasible way to promote antibiotic stewardship in the ICU and can be used as a strategy to reduce unnecessary patient exposure to broad-spectrum agents.

Keywords. antibiotic stewardship; critical care; infectious diseases; intensive care unit.

In 1955, major medical journals first started reporting on the emergence of antibiotic-resistant bacteria. At that time, an article published in *The Lancet* argued that, in addition to a number of harmful side effects potentially caused by antibiotics, their "indiscriminate use must accelerate the emergence of resistant strains of bacteria" [1–3]. Almost 60 years later, the United States government made combating antibiotic-resistant bacteria a national mission and by 2015, 48.1% of all hospitals nationally had implemented an antibiotic stewardship program [4, 5].

Infection is a leading cause of admission to the intensive care unit (ICU), with 1 study finding that more than half of all patients admitted on a given day were considered to be infected [6]. Even though patients with infection form the majority of admissions to the ICU, a dedicated ID consultation and stewardship team is not routinely implemented. Critically ill patients frequently receive empiric broad-spectrum antibiotics during their ICU stay, often with unpredictable changes in organ perfusion and fluid status, which can affect antibiotic pharmacokinetics, doses, and drug efficacy [7]. In 1 multicenter point prevalence study, 31% of ICU regimens were deemed inappropriate with respect to regimen chosen, as well as dosing and route of administration [8]. Inappropriate initial antimicrobial therapy can cause up to a 5-fold decrease in survival to hospital discharge while ID consultation has been shown to reduce mortality in hospitalized patients with severe sepsis and septic shock, and the close involvement of an ID consultant has

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been shown to lead to a reduction in antibiotic days of therapy (DOT) [9–13].

To further explore the effects of a hybrid ID consultation and stewardship program, an ID-CCM pilot program was designed in collaboration with the CCM service at the Jack D. Weiler Hospital of the Montefiore Medical Center (MMC). This service was introduced in August 2016 and included daily focused clinical rounds, antibiotic selection, dosing, stewardship, and teaching for clinical staff and trainees in addition to formal ID consultation for selected cases. The purpose of this study was to evaluate effects on antibiotic utilization and clinical outcomes in patients as a result of this multidisciplinary team approach between ID and CCM.

METHODS

This was a single-site retrospective cohort study, approved by the Institutional Review Board at MMC/Albert Einstein College of Medicine with waiver of informed consent. The intervention group included all patients admitted to an ICU from January 1, 2017 to December 31, 2017, after the introduction of the ID-CCM service. The control group included all patients admitted to the same units from January 1, 2015 to December 31, 2015. This time period was chosen as a comparator because the ID–Critical Care pilot program was initiated in the latter part of 2016 and the study aimed to include a period of a full calendar year to account for any seasonal variations in ICU admissions. The study population consisted of all patients age 18 and older admitted or transferred to the medical intensive care unit, cardiothoracic/surgical ICU, or the cardiology care unit, as well as patients seen in the emergency department and accepted to 1 of the above-listed units. The study excluded patients who died or were discharged within 24 hours of admission or were transferred to another facility within 24 hours of admission. For patients who had multiple ICU admissions, only the last admission was included in the analysis as the study design and statistical methods did not account for multiple observations for the same subject. This was also done to be conservative, as the patient may be more sick or frail than at the time of the earlier admissions. The identification of patients who fit the inclusion criteria and data on clinical outcomes were completed using Clinical Looking Glass (Emerging Health Information Technology, Yonkers, New York), a computerized health care surveillance software at MMC linked to the electronic health records [14]. Patient-specific data on antibiotic usage was obtained using EPIC pharmacy reports for administered antibiotics. Data were validated via chart review. Data collected included patient demographics, admitting diagnosis, comorbidities, laboratory values, antibiotic treatment, clinical outcomes, and discharge disposition. The primary outcomes were all-cause in-hospital mortality, antibiotic agents used, days of antibiotic therapy, and courses of antibiotic therapy (COT). The secondary outcomes were hospital length of stay, 30-day readmission, and 30-day mortality. We also looked at these outcomes in a subgroup of patients in whom infection was the primary admission diagnosis.

Statistical Analysis

Baseline demographics and key clinical variables were compared between the intervention group and the control group. No a priori power calculations were conducted. We studied all the patients satisfying inclusion/exclusion criteria who were admitted to the ICU during the intervention period. Demographic and clinical characteristics were tabulated by year (2017 vs 2015). Categorical variables were compared between 2017 and 2015 using χ^2 tests or Fisher exact tests, and continuous variables were compared using 2-sample *t* tests or Wilcoxon rank-sum tests, as appropriate. Rates of 30-day in-hospital mortality and all in-hospital mortality (among all patients) and rate of 30-day readmission and length of hospital stay (among those discharged alive) were similarly compared between the 2017 and 2015 cohorts. Fine and Gray competing risks models were used to analyze time from admission to mortality and time from admission to discharge alive, treating mortality and discharge alive as competing events [15]. Subdistribution hazard ratios and 95% confidence intervals were calculated comparing probability of mortality and probability of discharge alive between 2017 and 2015. Additional Fine and Gray models were adjusted for demographic and clinical characteristics that differed between the 2017 and 2015 cohorts at the level of $P < .1$. All analyses were repeated within the subsample of patients with a primary diagnosis of infection. A 2-sided α of .05 was used to determine statistical significance. Analyses were conducted in SAS version 9.4 software.

Data obtained from pharmacy were used to calculate the dose/number of antibiotics, courses of antibiotic therapy, and/or reduction in the number of days on antibiotics during ICU stay. Using Poisson regression analysis, we evaluated antibiotic utilization of each agent between the 2 groups, expressed as DOT per 1000 patient-days and number of courses per 1000 patient-days (with any gap of >3 days defined as a new COT). We defined a patient-day as the number of patients present in the facility at the same time on each calendar day of the month, summed across all days of the month [16].

RESULTS

A total of 3496 patients were included in the study, 1766 in the intervention group and 1730 patients in the control group. Baseline demographics were similar between the 2 groups (Table 1). The patients in the intervention group were more likely to have congestive heart failure (43.8% vs 38.8%, $P = .003$) and renal disease (35.7% vs 29.7%, $P = .0001$) compared with the control group. There was no difference in the overall median Charlson comorbidity score (3.0 vs 3.0, $P = .67$) and baseline presentation laboratory values of bilirubin, creatinine, and platelets between the 2 groups (Table 1).

Table 1. Full Sample of Index Intensive Care Unit Admissions in 2015 and 2017: Demographic and Clinical Characteristics

Characteristic	Total (N = 3496)	2015 (n = 1730)	2017 (n = 1766)	*P* Value[a]
Age, y, mean (SD)	64.4 (15.5)	63.9 (15.8)	64.9 (15.1)	**.0420**
Sex, No. (%)				**.0259**
Female	1617 (46.3)	833 (48.2)	784 (44.4)	
Male	1879 (53.7)	897 (51.8)	982 (55.6)	
Race/ethnicity, No. (%)				**.0321**
Hispanic	987 (28.2)	460 (26.6)	527 (29.8)	
Non-Hispanic black	887 (25.4)	442 (25.5)	445 (25.2)	
Non-Hispanic white	823 (23.5)	440 (25.4)	383 (21.7)	
Other/multiracial/unknown	799 (22.9)	388 (22.4)	411 (23.3)	
Infection primary diagnosis, No. (%)	884 (25.3)	449 (26.0)	435 (24.6)	.3686
Charlson comorbidity score, median (IQR)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.0–6.0)	.6732
Individual comorbidity, No. (%)				
Myocardial infarction	1070 (30.6)	538 (31.1)	532 (30.1)	.5322
Congestive heart failure	1445 (41.3)	672 (38.8)	773 (43.8)	**.0031**
Peripheral vascular disease	559 (16.0)	303 (17.5)	256 (14.5)	**.0149**
Cerebrovascular disease	447 (12.8)	245 (14.2)	202 (11.4)	**.0159**
Dementia	264 (7.6)	114 (6.6)	150 (8.5)	**.0331**
Chronic pulmonary disease	1198 (34.3)	606 (35.0)	592 (33.5)	.3480
Rheumatic disease	118 (3.4)	72 (4.2)	46 (2.6)	**.0108**
Peptic ulcer disease	169 (4.8)	92 (5.3)	77 (4.4)	.1868
Mild liver disease	379 (10.8)	205 (11.8)	174 (9.9)	.0576
Diabetes	1419 (40.6)	728 (42.1)	691 (39.1)	.0755
Hemiplegia or paraplegia	142 (4.1)	81 (4.7)	61 (3.5)	.0659
Renal disease	1144 (32.7)	513 (29.7)	631 (35.7)	**.0001**
Any malignancy	365 (10.4)	201 (11.6)	164 (9.3)	**.0242**
Moderate or severe liver disease	104 (3.0)	53 (3.1)	51 (2.9)	.7598
Metastatic solid tumor	143 (4.1)	83 (4.8)	60 (3.4)	**.0366**
AIDS/HIV	69 (2.0)	43 (2.5)	26 (1.5)	**.0313**
Bilirubin, median (IQR) (n = 224 missing)	.5 (.3–.8)	.5 (.3–.8)	.5 (.3–.9)	**.0148**
Creatinine, median (IQR) (n = 17 missing)	1.1 (.8–1.8)	1.1 (.8–1.8)	1.1 (.8–1.8)	.7149
Platelets, median (IQR) (n = 14 missing)	211.0 (158.0–275.0)	210.0 (159.0–274.0)	212.0 (158.0–276.0)	.7863

Values in bold are considered statistically significant.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

[a] *t* test, Wilcoxon rank-sum test, χ^2 test, or Fisher exact test.

Primary Outcomes

There was no difference between the intervention and control cohorts in the overall in-hospital mortality rate (15.2% vs 15.0%, *P* = .87) (Table 2). There was also no difference in risk of in-hospital mortality between the 2 groups both before and after adjusting for potential confounders using a Fine and Gray model with discharge alive treated as a competing event (Table 2; Table 3).

The 6 most commonly used broad-spectrum antibiotic agents—cefepime, daptomycin, linezolid, meropenem, piperacillin-tazobactam, and vancomycin—were included in the final analysis. During the intervention period, statistically significant reductions

Table 2. Full Sample of Index Intensive Care Unit Admissions in 2015 and 2017: In-hospital Mortality, LOS and Readmission for those Discharged Alive, and LOS for Patients Who Died in the Hospital

Full Sample	Total	2015	2017	*P* Value[a]
Mortality, No. (%)	N = 3496	n = 1730	n = 1766	
30-day in-hospital mortality	486 (13.9)	244 (14.1)	242 (13.7)	.7320
All in-hospital mortality	529 (15.1)	260 (15.0)	269 (15.2)	.8668
Discharged alive	n = 2967	n = 1470	n = 1497	
Hospital LOS (ie, time to discharge alive), median (IQR)	8.0 (4.0–14.0)	8.0 (4.0–14.0)	8.0 (4.0–14.0)	.9445
30-d readmission, No. (%)	523 (17.6)	262 (17.8)	261 (17.4)	.7814
Died in hospital	n = 529	n = 260	n = 269	
Hospital LOS (ie, time to mortality), median (IQR)	11.0 (5.0–19.0)	10.0 (4.0–18.5)	12.0 (5.0–20.0)	.2891

Abbreviations: IQR, interquartile range; LOS, length of stay.

[a]Wilcoxon rank-sum test, χ^2 test, or Fisher exact test.

Table 3. Full Sample: Fine and Gray (Competing Risks) Models of Time to Mortality and Time to Discharge Alive (N = 3496)

	Model 1		Model 2	
Mortality and Discharge	sHR (95% CI)	*P* Value	Adjusted sHR (95% CI)[a]	*P* Value
Outcome event = mortality (competing event = discharge alive)				
Year 2017 (reference = 2015)	1.01 (.85–1.20)	.9044	1.02 (.86–1.22)	.8018
Outcome event = discharge alive (competing event = mortality)				
Year 2017 (reference = 2015)	.99 (.92–1.06)	.7450	.97 (.90–1.05)	.4757

Abbreviations: CI, confidence interval; sHR, subdistribution hazard ratio.

[a]Adjusted for age, sex, race/ethnicity, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatic disease, mild liver disease, diabetes, hemiplegia or paraplegia, renal disease, any malignancy, metastatic solid tumor, AIDS/human immunodeficiency virus, and bilirubin (variables with $P < .1$ in Table 1).

in days of therapy were seen in cefepime (131 vs 101 DOT per 1000 patient-days, $P = .01$), piperacillin-tazobactam (268 vs 251 DOT per 1000 patient-days, $P = .02$), and intravenous vancomycin (265 vs 228 DOT per 1000 patient-days, $P = .01$). The utilization of other antibiotics including daptomycin, linezolid, and meropenem did not differ significantly (Figure 1). Statistically significant reductions in COT were seen for cefepime (131 vs 101 COT per 1000 patient-days, $P = .002$) and intravenous vancomycin (265 vs 229 COT per 1000 patient-days, $P = .005$) (Table 4; Table 5).

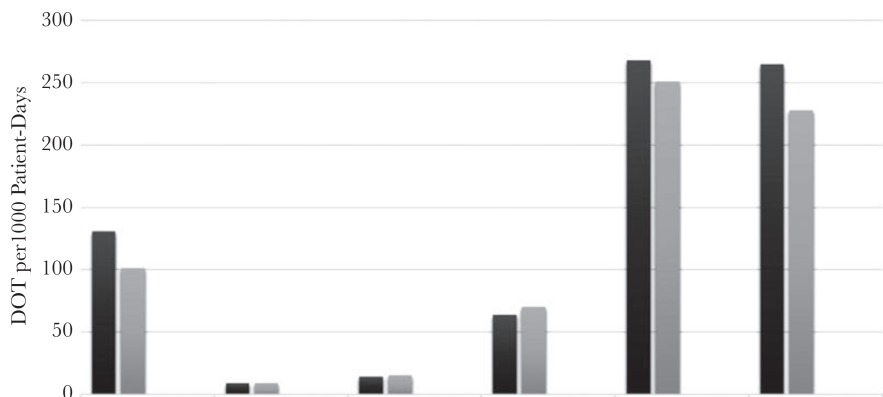
Secondary Outcomes

There was no difference in the 30-day in-hospital mortality rate between the 2 groups (13.7% vs 14.1%, $P = .73$). Of the patients discharged alive, there was no difference in median length of hospital stay (8.0 days vs 8.0 days, $P = .94$) or 30-day readmission rate (17.4% vs 17.8%, $P = .78$) (Table 2).

Patients With Infection as the Primary Diagnosis

Infection was the primary diagnosis in 884 patients (25.3%): 435 patients (24.6%) in the intervention group and 449 patients (26%) in the control group. Of these patients, 738 (83.5%) had the primary diagnosis of sepsis: 372 patients (85.5%) in the intervention group and 366 patients (81.5%) in the control group. Of the patients presenting with sepsis, the most frequent source was respiratory (50.5%). There was no difference in the overall median Charlson comorbidity score (4.0 vs 4.0, $P = .31$) and baseline presentation laboratory values of lactate, bilirubin, creatinine, and platelets between the 2 groups (Supplementary Table 1).

There was no difference in in-hospital mortality rate between the intervention and control groups (32.4% vs 31.8%, $P = .86$). There was no difference in risk of in-hospital mortality rate both before and after adjusting for potential confounders. Patients in the intervention group who were discharged alive had a longer median hospital length of stay (14 days vs 13 days, $P = .03$). There was no difference in 30-day in-hospital mortality rate (28.5% vs 28.7%, $P = .94$) or 30-day readmission rate among those discharged alive (21.4% vs 22.9%, $P = .67$) (Supplementary Tables 2 and 3).



	Cefepime*	Daptomycin	Linezolid	Meropenem	Piperacillin-Tazobactam*	Vancomycin*
■ 2015 DOT per 1000 Patient-Days	131	9	14	64	268	265
■ 2017 DOT per 1000 Patient-Days	101	9	15	70	251	228
Incidence rate ratio	0.77	1.00	1.11	1.09	0.94	0.86
P Value	<.01	.99	.4	.12	.02	<.01

Figure 1. Antibiotic utilization rates of most frequently used broad-spectrum agents pre- and postintervention. *Statistically significant, *P* value calculated using Poisson regression analysis. Abbreviation: DOT, days of therapy.

Table 4. Full Sample: Antibiotic Courses and Days of Therapy

Antibiotic	2015 Courses	2015 DOT	2015 DOT per 1000 Patient-Days	2017 Courses	2017 DOT	2017 DOT per 1000 Patient-Days
Cefepime	271	1231	131	219	1010	101
Daptomycin	34	81	9	24	87	9
Linezolid	27	128	14	30	152	15
Meropenem	120	601	64	145	702	70
Piperacillin-tazobactam	639	2511	268	634	2520	252
Vancomycin	915	2487	265	858	2291	229

Abbreviation: DOT, days of therapy.

Hospital-Acquired Infections

There was a decrease in the incidence of *Clostridioides difficile* infections, central line–associated bloodstream infections (CLABSIs), and catheter-associated urinary tract infections (CAUTIs). There were 24 cases of *C. difficile* in 2015 and 15 cases in 2017. There were 6 CLABSIs in 2015 and none in 2017. There were 11 CAUTIs in 2015 and 2 in 2017. Due to the small numbers in both years, we deferred statistical analysis, which was not feasible.

DISCUSSION

With this study, we found a decrease in the use of frequently prescribed broad-spectrum antibiotics without a negative impact on clinical outcomes in critically ill patients. Previous strategies to improve antibiotic utilization in critical care units have included formal infectious diseases consultation, verbal audit and feedback, prior approvals, antibiotic time-outs, and computer-assisted de-escalation strategies [11, 17, 18]. Our approach of incorporating a dedicated ID-CCM service proved to be another feasible way of promoting antibiotic stewardship in the ICU and can be used as a strategy to reduce unnecessary patient exposure to broad-spectrum agents.

The limitations of our study include the retrospective nature, only allowing for a comparison of a historical cohort with 1 year of data. We chose 2015 for the historical cohort because the ID-CCM service was initiated in the latter half of 2016 and we wanted to allow for a period of transition in order to gauge the full effect of this service. Moreover, we wanted to include the period of a full calendar year to account for any seasonal variations in ICU admissions. This service was introduced as an additional intervention to the antibiotic stewardship program that had been in effect at all campuses of MMC since 2013. The stewardship policies and clinical practices were largely unchanged during the time periods included in the study.

As it was not practical to perform a chart review on the 3496 patients included in this study, the specifics of antibiotic administration and de-escalation could not be obtained. With respect to the antibiotic use data, we were unable to calculate the denominator of 1000 days present, which is used as the denominator in the antimicrobial use module from National Healthcare Safety Network (NHSN), as our institution did not start submitting to NHSN until 2018. Furthermore, we were unable to calculate the standardized antimicrobial administration ratios, which would have allowed us to see the trends of antimicrobial use from month to month during the time period that we reviewed [16, 19]. Another limitation was that this study included a limited immunocompromised population as it was conducted at only 1 campus of our medical center, which has an oncology service but does not include transplant patients as the transplant service is at a different campus.

The strength of our study is that it demonstrates the impact of a successful stewardship approach when applied to a diverse population. Our intervention was institution specific and due to time and staffing restraints it was introduced at only 1 of the sites of our large academic medical center. This effort required the complete diversion of efforts of a full-time ID faculty to this service in order to incorporate daily rounding with ICU teams with ongoing partnership from pharmacy. Though it is

Table 5. Full Sample: Antibiotic Courses and Days of Therapy Incidence Rate Ratio

	Courses		DOT	
Antibiotic	IRR	*P* Value[a]	IRR	*P* Value[a]
Cefepime	0.75427037	**.001866**	0.76580032	**2.94×10^{-10}**
Daptomycin	0.65884697	.117799	1.0025048	.987821
Linezolid	1.0370739	.8931	1.1083728	.391836
Meropenem	1.1278179	.330366	1.0902218	.119984
Piperacillin-tazobactam	0.9260632	.170721	0.93671193	.020433
Vancomycin	0.87522239	**.005034**	0.85980809	**1.80×10^{-7}**

Values in bold are considered statistically significant.
Abbreviations: DOT, days of therapy; IRR, incidence rate ratio.
[a] *P*-Value calculated using Poisson regression analysis.

a time-intensive intervention, the incorporation of an ID specialist, whether a physician, pharmacist, or midlevel provider, is a feasible and worthwhile approach that can be implemented across many institutions. As we have shown in our study, it can make a meaningful impact on antibiotic utilization and can be a cost-effective intervention for a hospital system. Most importantly, despite the decrease in use of broad-spectrum antibiotics, our study showed no harm to patient care.

This hybrid approach is a feasible model, allowing for multidisciplinary collaboration between the ID, CCM, and pharmacy departments. Even though it was initially challenging to implement, it proved to be a reasonable way to promote antibiotic stewardship and appropriate antibiotic use in critical care units.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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